Aspergillus Endocarditis in Children: Case Report and Review of the Literature

Robyn J. Barst, MD, Alice S. Prince, MD, and Harold C. Neu, MD

From the Division of Cardiology and Infectious Diseases, Departments of Pediatrics and Medicine, College of Physicians & Surgeons, Columbia University, New York

ABSTRACT. *Aspergillus fumigatus* endocarditis developed in a 2½-year-old girl after repair of tetralogy of Fallot. There have been 14 other cases of *Aspergillus* endocarditis in children described in the literature. Fever and embolic phenomenon, particularly to the CNS, were the most common presenting manifestations. Consumptive coagulopathy developed in this patient as it has in other children and should suggest the diagnosis of *Aspergillus* endocarditis inasmuch as blood cultures are uniformly negative. Antemortem diagnosis was made in four of 15 patients. Only one patient survived the infection. Environmental surveillance is crucial when a case is encountered. Survival of the infected patient occurs only with early diagnosis and surgical removal of the infected tissue. *Pediatrics* 68:73–78, 1981; *Aspergillus endocarditis, consumptive coagulopathy, Aspergillus.*

Aspergillus endocarditis is a rare disease in adults and children. In the past ten years there has been an increase in this disease that has corresponded with the increase in open-heart surgery.[1] Although bacterial endocarditis is a well recognized complication of open-heart surgery, fungal infections of the endocardium frequently are unsuspected and are more difficult to diagnose. Endocarditis due to *Aspergillus fumigatus* was diagnosed post mortem in a 2½-year-old child after correction of tetralogy of Fallot—the third case of *Aspergillus* endocarditis observed at this institution in approximately 15 years.[2,3] We present this case and a review of the literature to call attention to this usually fatal complication of open-heart surgery.

CASE REPORT

D.A. was noted to have a tetralogy of Fallot abnormality in the first month of life, and she was admitted for elective total correction at age 2 11/12 years. During open-heart surgery a large right ventricular outflow patch was placed across the valve annulus, and the ventricular septal defect was repaired. Cardiopulmonary bypass time was two hours. Several units of blood and fresh frozen plasma were required intraoperatively. She received oxacillin and kanamycin perioperatively and postoperatively for five days but remained intermittently febrile. Bilateral pleural effusions were present, but thoracentesis fluid was sterile on routine cultures. She had M-mode and 2-D echocardiography which showed only pericardial effusion and a small right-to-left shunt at the atrial level.

On the eighth postoperative day, the patient was given aspirin for treatment of a suspected postpericardiotomy syndrome. All blood cultures were negative for bacteria and fungi. Slurred speech and generalized lethary were noted on the fourth postoperative day, but no focal neurologic deficits were found. An EEG performed two weeks later showed some slight asymmetry but was otherwise normal. She continued to be very irritable and was unable to speak clearly. On the 20th postoperative day her temperature reached 102 F, and she developed a right hemiparesis and loss of speech. Results of computed tomography were negative. WBC count remained between 17,000 and 22,000/cu mm with a predominance of polymorphonuclear cells; ESR (Westergren) was 5 and 10 mm/hr. During the next 24 hours she became progressively less responsive. Fulminant disseminated intravascular coagulation developed with fibrin split products of 21 gm/ml (normal 0 to 10 gm/ml). Results of laboratory studies were as follows: prothrombin time 116/11 sec; activated partial thromboplastin time (APTT) 175 seconds (normal control 62 seconds) fibrinogen 21 mg/100 ml; decreased factor VLL, 1% (normal 50% to 150%); factor V, 40% (normal 50% to 150%; factor IX, 4% (normal 50% to 150%); red cells on smear were remarkable for burr cells and schistocytes, thrombocytopenia (platelets decreased to 15,100/cu mm), and anemia (hemoglobin decreased from 11 to 8.5 mg/100 ml). She was treated with ampicillin, amikacin, corticosteroids, vasopressor agents, vitamin K, fresh frozen plasma, packed red blood cells, intubation, and peritoneal dialysis. Despite maximal supportive care, cardiac output decreased, acidosis progressed, and she died on the 22nd postoperative day.

Heart blood obtained at the postmortem examination

Received for publication July 11, 1980; accepted Oct 16, 1980.
Reprint requests to (H.C.N.) Department of Medicine, 630 W 168th St, New York, NY 10032.

grew *Aspergillus fumigatus*. This was confirmed by growth at 42 C, characteristic morphology, and speciation according to standard methods.[4] At autopsy *Aspergillus* thrombi were found obstructing both the tricuspid and the pulmonary outflow tract (Fig 1). The endocardium at the area of the closure of the ventricular septal defect was necrotic with acute inflammation and vegetations of *Aspergillus* on the surface. A muscular ventricular septal defect (not repaired at surgery) was found at autopsy. This provided a right-to-left shunt for septal emboli to enter the systemic circulation and embolize to the brain (Fig 2). *Aspergillus* emboli were found in the lung as well as in the brain (in the left middle cerebral distribution with microabscesses in the left side of the thalamus and substantia nigra). Emboli were not found in other organs.

EPIDEMIOLOGY

A thorough search was made to identify the source of the *Aspergillus* infecting this patient. Contaminated air and prolonged exposure of the heart during surgery were considered likely sources.[5] Because parts of the hospital were under construction, the potential for dissemination of *Aspergillus* was increased. We have observed a num-

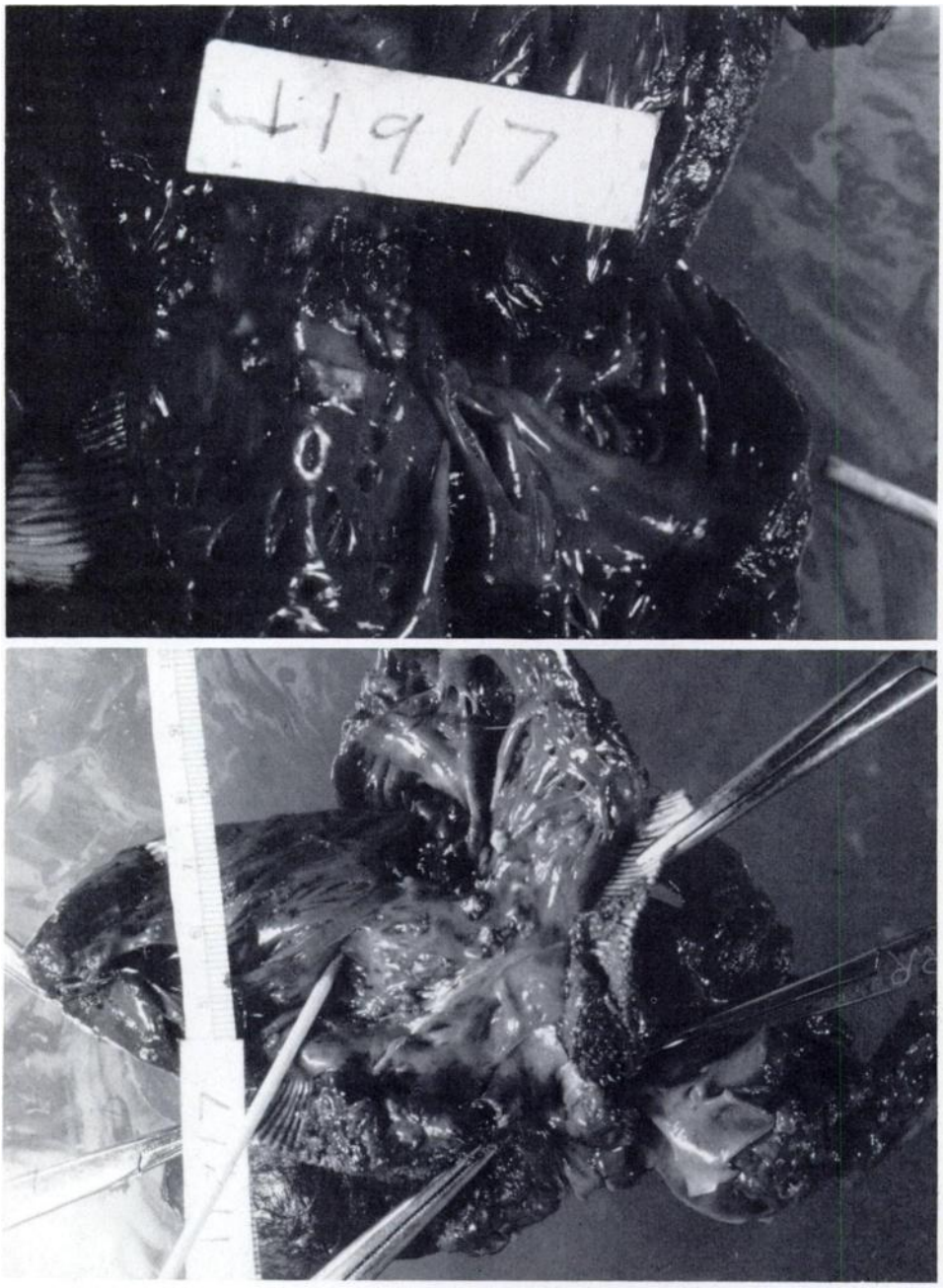

Fig 1. Fungating vegetation above patch in heart (top) and multiple sites of *Aspergillus* infection (bottom).

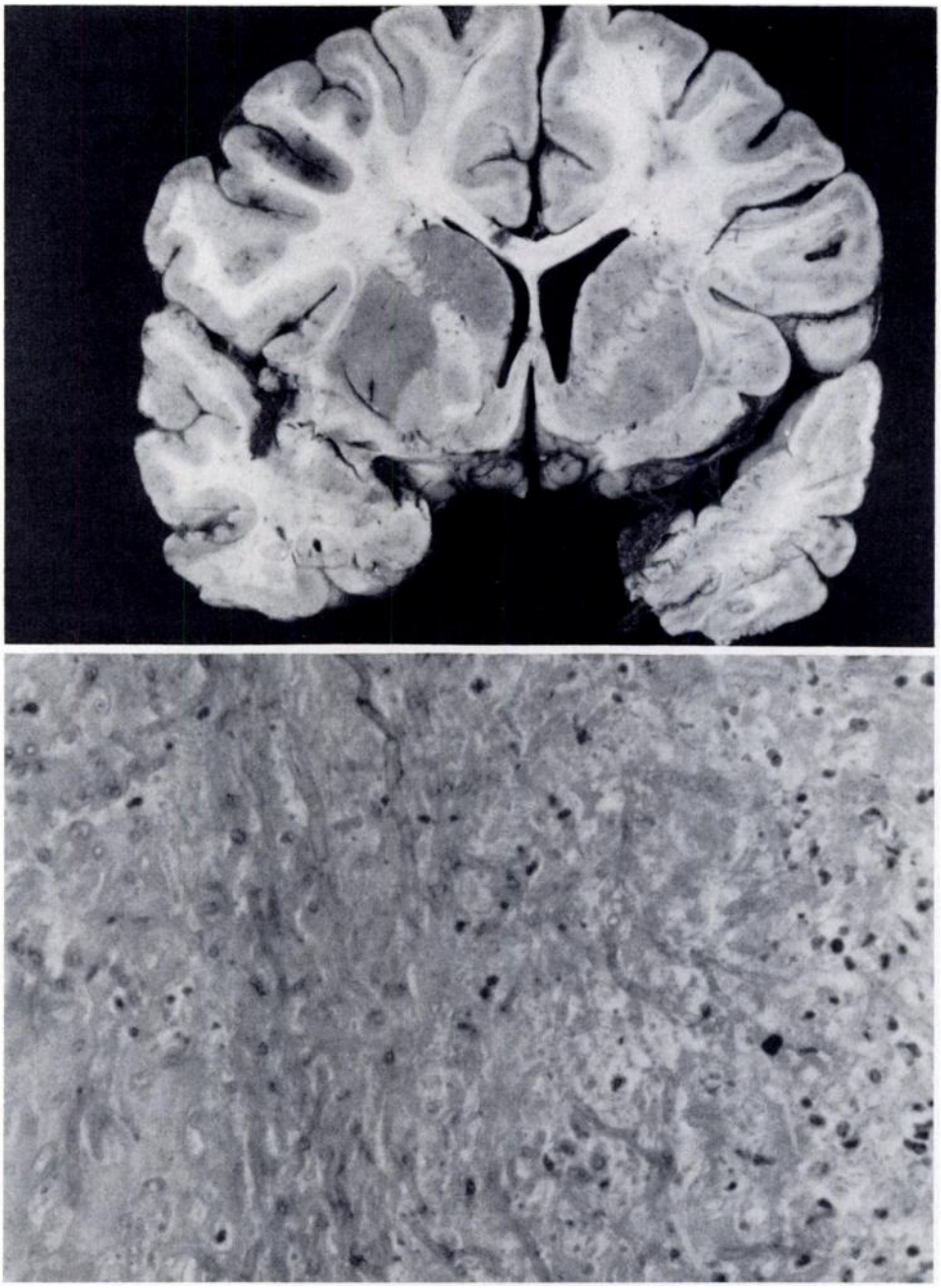

Fig 2. Foci of *Aspergillus* scattered throughout brain (top) and microscopic focus of *Aspergillus* in brain (bottom).

ber of *Aspergillus* infections in pediatric patients with hematologic malignancies who were in other areas of the hospital. The association of increased *Aspergillus* infection with hospital construction is well documented.[6] Our patients with underlying illness of leukemia developed cutaneous infections due to *A niger* and *A fumigatus* because of contamination of tape with *Aspergillus*. Although a pigeon roost on the air conditioning units outside the operating room was found, *Aspergillus* was not isolated from window ledges, from operating room surfaces, or from the circulating air when an Anderson air sampler was kept in place during surgical procedures and overnight. This patient had many indwelling catheters, often suspected as sources of fungal infection, but no central arterial or venous lines were in place after the seventh postoperative day, and there was no evidence of local infection when the lines were removed.

REVIEW OF LITERATURE

This patient demonstrates the cardinal features of *Aspergillus* endocarditis, which have been rec-

TABLE 1. Clinical Profile of Children with *Aspergillus* Endocarditis*

Patient No.	Age	Sex	Fungus	Associated Disease	Location of Vegetation	Premortem Diagnosis	Therapy	Outcome
1	8	M	*A fumigatus*	None	Left ventricle	No	None	Death
2	18	M	*A flavus*	Neutropenia, interstitial pneumonia	Right venticle	No	None	Death
3	51 days	M	*A fumigatus*	Erythroblastosis	Right and left ventricles	No	None	Death
4	2 mo	F	*A fumigatus*	Prematurity, cytomegalovirus infection	Left ventricle	No	None	Death
5	2 mo	F	*A flavus*	Unknown	Right atrium, right and left ventricles	No	None	Death
6	5	M	*Aspergillus* sp	CHD (ASD repair, mitral valvuloplasty)	Atrial septum	No	None	Death
7	9	M	*A niger*	CHD (aortic valvuloplasty for aortic stenosis)	Mitral valve, thrombus in aortic root	No	None	Death
8	15	M	*A terreus*	CHD (fascia lata repair of mitral leaflet for fibrinous body aneurysm)	Left atrium, posterior mitral valve leaflet over homograft	No	None	Death
9	13	M	*A fumigatus*	CHD (Starr-Edwards aortic prosthetic valve for AS/AI)	Aortic prosthetic valve	Yes	Amphotericin B, debridement of vegetations	Death†
10	14	F	*Aspergillus* sp	CHD (tricuspid valvuloplasty and mitral valve for TR/MR)	Annulus of prosthetic mitral valve	Yes	Valve replacement only	Well‡
11	13	F	*A flavus*	RHD (Starr-Edwards mitral prosthetic valve for MR)	Prosthetic mitral valve	Yes	Valve replacement, amphotericin B (10 days); total dose 115 mg	Death
12	11	F	*A fumigatus*	RHD (mitral prosthetic valve for MR)	Mitral valve, myocardial abscesses	No	None	Death
13	13	?	*A fumigatus*	CHD (TOF repair with Teflon patch closure of VSD)	Patch, separation of patch from ventricular septal defect (both ventricles)	No	None	Death
14	14	M	*A niger*	CHD (Teflon patch closure of VSD and unicusp aortic prosthetic valve for VSD with prolapsed aortic cusp)	Patch, prosthetic valve (both ventricles)	No	None	Death
15	2½	F	*A fumigatus*	CHD (TOF repair with Dacron outflow patch and VSD patch)	Right ventricle (both patches)	No	None	Death

* Abbreviations used are: CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; AS, aortic stenosis; AI, aortic insufficiency; TR, tricuspid regurgitation; MR, mitral regurgitation; RHD, rheumatic heart disease; TOF, tetralogy of Fallot.

† Patient was discharged but died suddenly months after therapy with amphotericin B.

‡ Alive at one year after surgery; *Aspergillus* endocarditis diagnosed prior to dissemination.

ognized mainly in adults after open-heart surgery: persistent fever, evidence of embolic phenomena, and consumption coagulopathy. There are 14 reported cases of *Aspergillus* endocarditis in children[7-12] in addition to this case report (Table 1). Children ranged in age from 51 days to 18 years; 60% were boys. Ten of the patients had organic heart disease and had undergone open-heart surgery in the previous ten months. The duration of symptoms that could be attributed to endocarditis after open-heart surgery ranged from two weeks to ten months. Eight patients had congenital heart disease, and two had rheumatic heart disease. Five patients had prosthetic valves placed during open-heart surgery and three had Dacron or Teflon patches placed during surgery. *Aspergillus* has infected synthetic as well as porcine valves.

Five patients with *Aspergillus* endocarditis did not have known heart disease. These included a 51-day-old premature infant with erythroblastosis,[11] a 2-month-old premature infant with congenital cytomegalovirus infection, an 18-year-old with pneumonia and neutropenia, and two patients, aged 2 months and 8 years, respectively, with no apparent underlying disease.

Presenting manifestations in the 15 patients are listed in Table 2. These signs and symptoms—fever, embolic phenomena, new murmurs, hepatosplenomegaly, petechiae, and CNS abnormalities—suggest endocarditis. Fungal endocarditis seems to produce major emboli more frequently.[1,3] There were no particular predisposing factors except open-heart surgery. Twelve of the 15 patients had received broad spectrum antibiotics prior to the clinically detected fungal infection and two had received corticosteroids.

Laboratory data have not helped to distinguish *Aspergillus* infection from other causes of endocarditis. Anemia is a frequent finding. Disseminated intravascular coagulation was present in our patient and has been reported as a complication of *Aspergillus* infection.[12] Blood cultures were obtained ante mortem in 13 of 15 cases. Only two positive cultures were reported, both after the patients had died. A third patient had a blood culture described as "overgrown by mold" and this information was ignored.

TABLE 2. Clinical Signs and Symptoms in 11 Open-Heart Surgery Patients with *Aspergillus* Endocarditis

Symptom	No. of Patients
Fever	11
Change in murmur	10
Emboli	9
Splenomegaly	7
Hepatomegaly	6
Petechiae	6
CNS abnormality	3

Antemortem diagnosis was made in four of 15 patients. The diagnostic specimen was an embolus in three patients and the artificial valve itself in one. Only one patient, a 14-year-old girl who developed severe mitral insufficiency after mitral valve replacement, survived the infection.[10] She was taken back to the operating room where vegetations were found unexpectedly on the valve and the valve was replaced. She had no dissemination of the *Aspergillus,* and although she received no treatment, she is the sole survivor of this infection. The other three patients in whom the condition was diagnosed prior to death all had disseminated disease. One was treated with valve replacement and amphotericin B; the other two were treated with amphotericin B alone.

Pathologic reports have shown involvement of the left side of the heart in eight patients, right side in two patients, and both sides in five patients. Fungi were identified microscopically and cultured in vegetations or emboli from all of the patients. In the ten patients reported for whom autopsy data are available there was evidence of embolic disease. The involved organs included: brain, kidneys, spleen, extremities, lungs, liver, thyroid, eyes, meninges, jejunum, and in one case "every organ." Most frequently involved were brain (9/10 patients), kidney (6/10 patients), spleen (4/10 patients), extremities (3/10 patients), and lung (2/10 patients).

The number of isolates of each *Aspergillus* species were: *A fumigatus*, 7; *A flavus*, 3; *A niger*, 2; *A terreus*, 1; and two unspeciated *Aspergillus.* There were no clinically pathologically distinctive features related to species.

DISCUSSION

The prevalence of *Aspergillus* endocarditis has increased with the increase in open-heart surgery. As this disease is almost always fatal (93% mortality), further efforts are needed to prevent it whenever possible or to diagnose the infection in the early stage when it can be treated successfully.

Unlike *Candida* endocarditis, which usually is due to nonsurgical sources of infection, ie, arterial and venous catheters, the most likely source of *Aspergillus* infection after open-heart surgery is airborne inoculation of the heart during the operation.[5] The presence of foreign material, such as valves and patches of either synthetic or porcine heterograft material,[11] may prevent normal host defenses from clearing the organisms before infection develops. *Aspergillus* proliferates and forms large mesh-like fungal masses that readily break off

and embolize. They lodge in distant organs, occasionally providing an accessible peripheral lesion which, if submitted to biopsy, can yield the diagnosis. The fungal mass in the heart, with its intricate rough surfaces, provides a nidus for hemolysis and the development of consumption coagulopathy.[11,12] Although *Aspergillus* infects as an opportunist, it readily invades, eroding through synthetic as well as natural tissues.

Echocardiography has proved helpful in the diagnosis of bacterial endocarditis in selected patients, particularly when the 2-D technique is used.[13] Our patient underwent both M-mode and 2-D echocardiography on two occasions, and vegetations were not visualized because these were at the patch area. There are no reports of *Aspergillus* endocarditis diagnosed by echocardiography.

Peripheral blood cultures are rarely positive for *Aspergillus*. This is true irrespective of the type of antimicrobial media used to culture for the organism. *Aspergillus* will grow in broth medium and on agar. It does not require supplements to standard media that are used to recover bacteria. Whether cultures will become positive more rapidly in dimorphic media has not been established. Use of vented bottles and incubation at 22, 30, and 37 C may result in earlier growth of some *Aspergillus* species, but *A fumigatus* will grow even at 42 C. Why the heart blood obtained at autopsy grew the organism when peripheral blood cultures were negative has not been explained.

The role of serology in diagnosing endocarditis due to *Aspergillus* is unknown as *Aspergillus* precipitin serology was not performed in any of the reported cases. This test has proved useful in the diagnosis of systemic infection due to *Aspergillus* when performed by some groups[14] but not by others.

Treatment of this disease is also problematic. Amphotericin B has inhibitory activity against *Aspergillus* in vitro, but its usefulness in animal model experiments of *Aspergillus* infection is less impressive. There are reports of the combined use of amphotericin B and 5-fluorocytosine or amphotericin B and rifampin,[15] but the evidence that these programs are effective is not convincing. It is clear that the best results will be obtained if all of the infected material can be removed. Antifungal agents must be considered as adjuncts to cover microscopic foci of infection. Because almost all patients had disseminated disease at the time of the diagnosis, the combination of valve replacement and amphotericin B is the best available therapy.

In summary, *Aspergillus* endocarditis should be one of the diseases considered in the patient with unexplained fever or signs of emboli after open-heart surgery and whose blood cultures are negative for bacteria. Antemortem diagnosis can be made from biopsy of an embolus and it is hoped that aggressive early treatment can decrease the mortality associated with this infection. Epidemiologic studies should be undertaken in the operating room to determine whether there is a source of the *Aspergillus* so as to prevent the outbreaks that were seen in the 1960s and outbreaks in hospitals in which cardiac surgical suites were under construction.[3]

REFERENCES

1. Walsh TJ, Hutchins GM, Bulkley BH, et al: Fungal infections of the heart: Analysis of 51 autopsy cases. *Am J Cardiol* 45:357, 1980
2. Cherubin CE, Neu HC: Infective endocarditis at The Presbyterian Medical Center in New York City from 1938–1967. *Am J Med* 51:83, 1971
3. Garvey GG, Neu HC: Endocarditis: an evolving disease. *Medicine* 57:105, 1978
4. Hadley ID, Trandel J, Coyle MB: Practical methods for culture and identification of fungi in the clinical microbiology laboratory, Cumitech II, in *Proceedings of the American Society of Microbiology*. Washington, DC, American Society of Microbiology, 1980, pp 1–17
5. Gage AA, Dean DC, Schimert G, et al: *Aspergillus* infection after cardiac surgery. *Arch Surg* 101:384, 1970
6. Anrow PM, Anderson RL, Mainous PD, et al: Pulmonary aspergillosis during hospital renovation. *Am Rev Respir Dis* 118:49, 1978
7. Kammer RB, Utz JP: Aspergillus species endocarditis. *Am J Med* 56:506, 1974
8. Rubinstein E, Noriegg ER, Simberkoff MS, et al: Fungal endocarditis: Analysis of 24 cases and review of the literature. *Medicine* 54:331, 1975
9. Amoury RA, Bowman FO, Malm JR: Endocarditis associated with intracardiac prosthesis. *J Thorac Cardiovasc Surg* 51:36, 1966
10. Hairston P, Lee WH: Management of infected prosthetic heart valves. *Ann Thorac Surg* 9:229, 1970
11. Luke JL, Bolande RP, Gross S: Generalized aspergillosis and *Aspergillus* endocarditis in infancy. *Pediatrics* 31:115, 1963
12. Doughten RM, Pearson HA: Disseminated intravascular coagulation associated with Aspergillus endocarditis. *J Pediatr* 73:576, 1968
13. Dillon T, Meyer RA, Korfhagen JC, et al: Management of infective endocarditis using echocardiography. *J Pediatr* 96: 552, 1980
14. Young RC, Bennett JE: Invasive aspergillosis: Absence of detectable antibody response. *Am Rev Respir Dis* 104:710, 1971
15. Drexler L, Rytel M, Keelan M, et al: *Aspergillus terreus* infective endocarditis on a porcine heterograft valve. *J Thorac Cardiovasc Surg* 79:269, 1980